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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(57) Abstract

There is disclosed the use of: (i) ExB, CxxB or VxxB free from whole toxin; (ii) an agent other than ExxB or CxxB, having GM1-binding activity, or an agent other than VxxB having GM2-binding activity, or (iii) an agent tawing an effect on intracellular signalling events mediated by GM1-binding or G03 binding; as an immunomodulator for a vaccine against infectious diseases.

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Inter anal Application No PCT/GB 99/01461

Relevant to claim No.

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A. CLASSIFICATION OF SUBJECT MATTER IPC 6 A61K39/12 A61K38/16 A61K39/245 A61K39/385

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Category * Citation of document, with indication, where appropriate, of the relevant passages WO 97 02045 A (UNIVERSITY OF BRISTOL)

23 January 1997 (1997-01-23)

IPC 6 A61K C07K

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

	cited in the application page 44 -page 46		
Υ	NASHAR T O ET AL: "Modulatio activation by the B subunit o coli enterotoxin: receptor in up-regulates MHC class II, 87 and ICAM-1." IMUNNOLOGY, (1997 AUG) 91 (4) XP002123821 the Whole document	f Escherichia teraction , CD40, CD25	1-36
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° Special c	ther documents are listed in the continuation of box C. ategories of cited documents	Patent lamily members are liste "T" later document published after the in	temational filing date
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Inte: anal Application No PCT/GB 99/01461

C.(Continua	ation) DOCUMENTS CONSIDERED TO BE RELEVANT			
ategory *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
(HIRST T R ET AL: "Cholera toxin and related enterotoxins as potent immune modulators." SOCIETY FOR APPLIED BACTERIOLOGY SYMPOSIUM SERIES, (1998) 27 26S-34S, XPO00856429 the whole document	1-36		
(EP 0 372 928 A (UNIVERSITY OF LEICESTER) 13 June 1990 (1990-06-13) claims 1-14	1,24, 28-30		
X	US 5 241 053 A (FUJISAWA Y. ET AL.) 31 August 1993 (1993-08-31) the whole document	1,24, 28-30		
X	ZHANG T ET AL: "ORAL IMMUNIZATION WITH THE DODECAPEFTIDE REPEAT OF THE SERINE—RICH ENTANCES HISTOLYTICA PROTEIN (SREHP) FUSED TO THE CHOLERA TOXIN B SUBUNIT INDUCES A MUCOSAL AND SYSTEMIC ANTI—SREHP ANTIBODY RESPONSE" INFECTION AND IMMUNITY, US, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, vol. 63, no. 4, page 1349–1355 XP000645273 ISSN: 0019–9567 the whole document	1,22,24, 26,28-30		
Р,Х	WILLIAMS N A ET AL: "Immune modulation by the cholera-like enterotoxins: from adjuvant to therapeutic." IMMUNOLOGY TODAY, (1999 FEB) 20 (2) 95-101, XP002123822 the whole document	1-36		
P,X	NASHAR T 0 ET AL: "Importance of receptor binding in the immunogenicity, adjuvanticity and therapeutic properties of cholera toxin and Escherichia coli heat-labile enterotoxin." MEDICAL MICROBIOLOGY AND IMMUNOLOGY, (1998 JUN) 187 (1) 3-10, XP000857029 the whole document	1-36		
Ρ,Χ	RICHARDS C M ET AL: "Induction of mucosal immunity against herpes simplex virus type 1 in the mouse protects against ocular infection and establishment of latency." JOURNAL OF INFECTIOUS DISEASES, (1998 JUN) 177 (6) 1451-7. , XPO02123823 cited in the application the whole document	1-36		

Inter mail Application No PCT/GB 99/01461

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT Relevant to claim No. Category * | Citation of document, with indication, where appropriate, of the relevant passages 1-36 Ε EP 0 919 243 A (DUPHAR INTERNATIONAL RESEARCH) 2 June 1999 (1999-06-02) the whole document 1-36 WO 99 36088 A (MAXIM PHARMACEUTICALS) Ε 22 July 1999 (1999-07-22) the whole document

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I...crnational application No.

PCT/GB 99/01461

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)
This international Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely: Remark: Although claims 1-23,30,31,34 and 35 are directed to a methodof treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful international Search can be carried out, specifically:
Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple invertions in this international application, as follows:
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
As all searchable claims could be searched without effort justifying an additional fee, this Authority did not linvite payment of any additional fee.
As only some of the required additional search free were timely paid by the applicant, this International Search Report covers only those claims for which free were paid, specifically claims Nos.:
No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the datims; it is covered by claims Nos.:
Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

information on patent family members

Inte onal Application No PCT/GB 99/01461

Patent document cited in search repor	t	Publication date		atent family member(s)	Publication date
WO 9702045	Α	23-01-1997	AU	6314296 A	05-02-1997
			CA	2225788 A	23-01-1997
			CN	1192693 A	09-09-1998
			CZ	9800012 A	17-06-1998
			EP	0841939 A	20-05-1998
			HU	9900147 A	28-05-1999
			JP	11508586 T	27-07-1999
			NO	980005 A	05-03-1998
			PL	324424 A	25-05-1998
FP 372928	Α	13-06-1990	AU	4754490 A	26-06-1990
			CA	2004738 A	07-06-1990
			WO	9006366 A	14-06-1990
			PT	92511 A	29-06-1990
US 5241053	Α	31-08-1993	NONE		
EP 919243	Α	02-06-1999	AU	1875099 A	15-06-1999
El JIJE10		02 00 1777	WO	9926654 A	03-06-1999
W0 9936088	Α	22-07-1999	AU	2232399 A	02-08-1999